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What's in a Name? Chromosome 22q Abnormalities and the DiGeorge, Velocardiofacial, and Conotruncal Anomalies Face Syndromes

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Long ago in India, three blind men, who had never seen an elephant since they were blind, went to the palace of the Rajah, where there were many elephants. They touched the elephant with their hands and set out to describe it. The first blind man touched the elephant's side and said, "An elephant is like a wall." The second blind man touched the elephant's leg and said, "An elephant is like a tree." The third blind man touched the elephant's ear and said, "An elephant is like a fan." Then, the blind men began shouting and arguing about what an elephant must be like and could not agree. The Rajah was awakened by the shouting and commanded the blind men to be quiet. The Rajah spoke in a kind voice and said, "The elephant is a big animal. Each man only touched one part. You must put the parts together to find out what an elephant is truly like."

Paraphrase of an Anonymous Indian Fable

The recent advances in our understanding of the phenotype associated with deletion of the DiGeorge Chromosome Region (DGCR) at 22q11.2 are in many ways analogous to the fable about the blind men and the elephant. Originally described as three distinct phenotypes (DiGeorge (DG) syndrome, velocardiofacial (VCF) syndrome, and the conotruncal anomalies face (CTAF) syndrome), it is now clear that there is only a single broad and variable phenotype associated with deletion of the DGCR [Lindsay et al., 1995; Wulfsberg et al., 1995; Leana-Cox et al., 1995]. As in the fable, distinguished clinicians approached this phenotypic "elephant" from different perspectives and provided three separate, although overlapping descriptions. Our analogy to this fable is not to imply some "blindness" on the part of these clinicians, but rather to point out the well-known difficulty in delineating the indistinct phenotypic boundaries of a syndrome until a genetic or biochemical marker for the condition is available. The recent availability of a fluorescent in situ hybridization (FISH) probe to detect deletion of the DGCR now allows delineation of the broad phenotype of our "elephant" which spans from lethal DG phenotypes through the intermediate VCF and CTAF phenotypes to the newly recognized "mild" phenotype consisting of only developmental delays and subtle facial abnormalities [Lindsay et al., 1995, Wulfsberg et al., 1995; Driscoll et al., 1995; Leana-Cox et al., 1995].

The original description of the DG "syndrome" grew out of a discussion at an annual meeting of the Society for Pediatric Research-American Pediatric Society in 1962 and was published by Cooper et al. [1965] and DiGeorge [1965]. This developmental field defect of the upper branchial arches is characterized by absent or hypoplastic thymus and parathyroid glands, and conotruncal cardiac malformations [DiGeorge, 1965]. Because of the recognition of a few rare but differing causes for the DiGeorge phenotype, including del (10p) [Greenberg et al., 1988, Monaco et al., 1991; Lai et al., 1992], del (4)(q21.3-q25) [Fukushima et al., 1992], fetal alcohol exposure [Ammann et al., 1982] and fetal isotretinoin exposure [Lammer et al., 1985], it is sometimes referred to as the DG sequence. However, since over 90% of all reported cases of the DG phenotype are due to deletion of the DGCR [Carey et al., 1992], the term "DG sequence" will likely be used less frequently.

In 1981, Shprintzen, working in a cleft lip/cleft palate clinic, recognized patients with a multiple malformation syndrome whose component manifestations included velopharyngeal insufficiency or cleft palate, conotruncal cardiac anomalies, learning disabilities, and a characteristic facial appearance [Sphrintzen et al., 1981]. Unselected groups of VCF patients have shown DGCR deletions in 68% to 81% of patients [Driscoll et al., 1993; Lindsay et al., 1995], although Sphrintzen [1994] has concluded that all typical VCF syndrome patients are linked to chromosome 22q11.2 abnormalities.

Meanwhile in Japan, Kinouchi et al. [1976] and later Takao et al. [1980] and Shimizu et al. [1984] delineated a new syndrome characterized by conotruncal cardiac anomalies, an abnormal face and developmental delays:

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the CTAF syndrome. Over 85% of these patients are now known to have DGCR deletions [Matsuoka et al., 1994; Burn et al., 1993]. Thus, DGCR deletions have become the common causal denominator for most cases of these three historically separate phenotypes. It is likely that for patients with similar phenotypes, but without 22q11.2 abnormalities, a different cause will be identified in the near future.

It was logical to hypothesize that this broad, apparently overlapping phenotype might represent a contiguous gene deletion syndrome, as first proposed for the DG syndrome by Schmickel [1986]. This is now considered unlikely because deletion mapping studies have shown no correlation between deletion size and phenotype [Motzkin et al., 1993; Morrow et al., 1995; Driscoll et al., 1995]. More importantly, inherited deletions, which appear to be stably transmitted, result in different expressions of the wide and continuous phenotypic spectrum within the same family [Driscoll et al., 1995; Leana-Cox et al., 1996; McLean et al., 1993]. Finally, a mother and daughter with typical DG/VCF syndrome have a balanced translocation through the DGCR supporting a current hypothesis that interruption of only a single gene is responsible for this variable syndrome [Demczuk et al., 1995; Budarf et al., 1995].

A number of patients with DGCR deletions were diagnosed with other recognized phenotypes prior to deletion studies including apparent isolated conotruncal malformations [Goldmuntz et al., 1993], the CHARGE "association" [Emanuel et al., 1992] and the Opitz GBBB syndrome [McDonald-McGinn et al., 1995]. That other diagnoses might be suspected in DGCR deletion patients is not surprising given its broad and often subtle phenotype. Since the DGCR deletion phenotypic spectrum includes many "mildly" affected individuals [Lindsay et al., 1995; Leana-Cox et at., 1995], it is important to consider this diagnosis in individuals presenting with only developmental delay and subtle facial abnormalities, but without any of the cardinal findings of the DG, VCF, or CTAF syndromes. Additionally, individuals with apparently similar phenotypes including the CHARGE "association" or hypertelorism syndromes (i.e., Opitz GBBB syndrome, Aarskog syndrome, and oto-palatal-digital syndromes) should be considered for DGCR deletion testing. Familial cases, as exemplified by the report of Leana-Cox et al. [1996] in this issue of the Journal have been especially valuable in defining the phenotypic boundaries of this disorder.

When patients, initially diagnosed with another recognized multiple malformation syndrome, are found to have DGCR deletions, it can be difficult to decide if the initial diagnosis was "inaccurate" and should be corrected, or if there is heterogeneity, with "some cases" due to DGCR deletions. Since the correlation between DGCR deletion and its phenotypic spectrum is rapidly and precisely being defined by hundreds of reported cases, we think this will diminish as an issue.

The rapid changes in our understanding of the phenotypes associated with DGCR deletions brings up the obvious but difficult question of what to call the "elephant." To call attention to the continuous phenotype and shared cause of DG, VCF and CTAF syndromes due to DGCR deletions, Wilson et al. [1993] proposed the use of the acronym CATCH 22 (**C**ardiac abnormalities, **A**bnormal face, **T**hymic hypoplasia, **C**left palate, **H**ypocalcemia, and deleted chromosome **22**). This acronym has value in that it does away with separate phenotypic names and stresses the single broad phenotype of this disorder. Unfortunately, this term has negative connotations from the book of the same name [Heller, 1962] and has come to be defined in the English language as "a paradox in a law, regulation, or practice that makes one a victim of its provisions no matter what one does" [Guralnik, 1986]. For this reason, most clinicians think this is an insensitive term for use when counseling families with this disorder and we strongly recommend its dismissal. The term "del 22q11.2 syndrome", while emotionally neutral, does not confer any phenotypic information and may prove inaccurate, as some individuals with this syndrome may in the future be shown to have single gene mutations in this area. It has been proposed that the compound term "DiGeorge/velocardiofacial (DG/VCF) syndrome" is a reasonable compromise in referring to this condition, as it calls attention to the phenotypic spectrum using the most familiar historical names [Wulfsberg et al., 1995]. However, we think it may be premature to try to establish uniform nomenclature for this disorder as our understanding is still evolving, and time, general use, and new discoveries may need to occur before a single final name for this "elephant" is established.

REFERENCES

Ammann AJ, Wara DW, Cowan MF, Banett DJ, Stiehm ER (1982): The DiGeorge syndrome and the fetal alcohol syndrome. AJDC 136:986–988.

Budarf ML, Collins J, Gong W, Roe B, Wang Z, Bailey LC, Sellinger B, Michaud D, Driscoll DA, Emanuel BS (1995): Cloning a balanced translocation associated with DiGeorge syndrome and identification of a disrupted candidate gene. Nature Genet 10:269–278.

Burn J, Takao A, Wilson D, Cross I, Momma K, Wadey R, Scambler P, Goodship J (1993): Conotruncal anomaly face syndrome is associated with a deletion within chromosome 22q11. J Med Genet 30: 822–824.

Carey AH, Kelly D, Halford S, Wadey R, Wilson D, Goodship J, Burn J, Paul T, Sharkey A, Dumanski J, Nordenskjold M, Williamson R, Scambler PJ (1992): Molecular genetic study of the frequency of monosomy 22q11.2 in DiGeorge syndrome. Am J Hum Genet 51: 964–970.

Cooper MD, Peterson RDA, Good RA (1965): A new concept of the cellular basis of immunology. J Pediatr 67:907–908.

Demczuk S, Aledo R, Zucman J, Delattre O, Desmaze C, Dauphinot L, Jalbert P, Rouleau GA, Thomas G, Aurias A (1995): Cloning of a balanced translocation breakpoint in the DiGeorge syndrome critical region and isolation of a novel potential adhesion receptor gene in its vicinity. Hum Molec Genet 4:551–558.

DiGeorge AM (1965): Discussions on a new concept of the cellular basis of immunology. J Pediatr 67:907.

Driscoll DA, Salvin J, Sellinger B, Budarf ML, McDonald-McGinn, Zackai EH, Emanuel BS (1993): Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: Implications for genetic counselling and prenatal diagnosis. J Med Genet 30:813–17.

Driscoll DA, Li M, Chien P, Capuano S, Zackai EH, McDonnald-McGinn DM, Christensen KM, Cuneo BF, Saal HM, Gold R, Spector EB, Emanuel BS, Budarf ML (1995): Familial 22q11 deletions: Phenotypic variability and determination of deletion boundaries by FISH. Am J Hum Genet 57:A33.

Emanuel BS, Budarf ML, Selliger B, Goldmuntz E, Driscoll DA (1992): Detection of microdeletions of 22q11.2 with flourescence in situ hybridization (FISH): Diagnosis of DiGeorge syndrome (DGS), velo-cardio-facial (VCF) syndrome, CHARGE association and conotruncal cardiac malformations. (Abstract) Am J Hum Genet 51 (suppl.): A3.

Fukushima Y, Ohashi H, Wakui K, Nishida T, Nakamura Y, Hoshino K, Ogawa K, Ohishi T (1992): DiGeorge syndrome with del(4)(q21.3q25): Possibility of the fourth chromosome region responsible for DiGeorge syndrome. Am J Hum Genet 51:A80.

Goldmuntz E, Driscoll D, Budarf ML, Zackai EH, McDonnald-McGinn DM, Biegel JA, Emmanuel BS (1993): Microdeletions of chromosomal region 22q11 in patients with congenital conotruncal cardiac defects. J Med Genet 30:807–812.

Greenberg F, Elder FFB, Haffner P, Northrup H, Ledbetter DH (1988): Cytogenetic findings in a prospective series of patients with DiGeorge anomaly. Am J Hum Genet 43:605–611.

Guralnik DB (1984): "Webster's New World Dictionary of the American Language." New York: Simon and Schuster, Inc., p 224.

Heller J (1962): Catch 22. London: Jonathan Cape.

Kinouchi A, Mori K, Ando M, Takao A (1976): Facial appearance of patients with conotruncal anomalies. Pediatr Jpn 17:84.

Lai MMR, Scriven PN, Ball C, Berry AC (1992): Simultaneous partial monosomy 10p and trisomy 5q in a case of hypoparathyroidism. J Med Genet 29:586–588.

Lammer EJ, Chen DT, Hoar RM, Agnish ND, Denke PJ, Braun JT, Curry CJ, Fernhoff PM, Grix AW, Jr, Lott IT, Richard JM, Sun SC (1985): Retinoic acid embryopathy. N Engl J Med 313:215–216.

Leana-Cox J, Pangkanon S, Supovitz KR, Curtin MS, Wulfsberg EA (1995): Phenotypic variability associated with del(22)(q11.2): A report of five familial cases. Am J Hum Genet 57:A95.

Lindsay EA, Greenberg F, Shaffer LG, Shapira SK, Scambler PJ, Baldini A (1995): Velo-cardio-facial syndrome: Frequency and extent of 22q11 deletions. Am J Med Genet 56:191–197.

Matsuoka R, Takao A, Kimura M, Imamura S, Kondo C, Joh-o K, Ikeda K, Nishibatake M, Ando M, Momma K (1994): Confirmation that the conotruncal anomaly face syndrome is associated with a deletion within 22q11.2. Am J Med Genet 53:285–289.

McDonald-McGinn DM, Driscoll DA, Bason L, Christensen K, Lynch D, Sullivan K, Canning D, Zavod W, Quinn N, Rome J, Paris, Y, Weinberg P, Clark BJ, Emanuel BS, Zakai EH (1995): Autosomal dominant "Opitz" GBBB syndrome due to a 22q11.2 deletion. Am J Med Genet 59:103–113.

McLean SD, Saal HM, Spinner NB, Emanuel BS, Driscoll DA (1993): Velo-cardio-facial syndrome: Intrafamilial variability of the phenotype. AJDC 147:1212–1216.

Monaco G, Pignata C, Rossi E, Mascellaro O, Cocozza S, Ciccimarra F (1991): DiGeorge anomaly associated with 10p deletion. Am J Med Genet 39:215–216.

Morrow B, Goldberg R, Carlson C, Das Gupta R, Sirotkin H, Collins J, Dunham I, O'Donnell H, Scambler P, Shprintzen R, Kucherlapati R (1995) Molecular definition of the 22q11 deletions in velocardio-facial syndrome. Am J Med Genet 56:1391–1405.

Motzkin B, Marion R, Goldberg R, Shprintzen R, Saenger P (1993): Variable phenotypes in velocardiofacial syndrome with chromosomal deletion. J Pediatr 123:406–410.

Schmickel RD (1986): Contiguous gene syndromes: A component of recognizable syndromes. J Pediatr 109:231–241.

Shimizu T, Takao A, Ando M, Hirayama A (1984): Conotruncal face syndrome: Its heterogeneity and association with thymus involution. In Nora JJ and Takao A (eds.): "Congenital Heart Disease: Causes and Processes." Mount Kisco, N.Y.: Futura Publishing, pp. 29–41.

Shprintzen RJ, Goldberg RB, Young D, Wolford L (1981): The velocardio-facial syndrome: A clinical and genetic analysis. Pediatr 67: 167–172.

Shprintzen RJ (1994): Velocardiofacial syndrome and DiGeorge sequence (letter). J. Med Genet 31:423–424.

Takao A, Ando M, Cho K, Kinouchi A, Murakami Y (1980): Etiologic categorization of common congenital heart diseases. In Van Praagh R and Takao A (eds): "Etiology and Morphogenesis of Congenital Heart Disease." Mount Kisco: NY. Futura Publishing, pp 261–269.

Wilson DI, Burn J, Scambler P, Goodship J (1993): DiGeorge syndrome: Part of CATCH 22. J Med Genet 30:852–856.

Wulfsberg EA, Pangkanon S, Supovitz KR, Curtin MS, Leana-Cox J (1995): What's in a name? Report of five deletion 22q11.2 families with comparison to familial DiGeorge and velocardiofacial syndromes. XVI David W. Smith Workshop on Malformations and Morphogenesis. Big Sky, Montana, July 30–August 3, 1995.